## REMARKS

Claims 1, 2, 4, 10-14, 16, 18-20, 22, 23, 32-34, 36, 44-47, 60, 61, 68, 88, and 90-93 were pending in the application. Of these, claims 1, 2, 4, 10-14, 16, 18-20, 22, 23 and 32-34 had been withdrawn from consideration by Applicants, but the Office rejoined these claims and examined them.

Thus, Claims 1, 2, 4, 10-14, 16, 18-20, 22, 23, 32-34, 36, 44-47, 60, 61, 68, 88, and 90-93 were examined and rejected.

The following claims are being canceled: 1, 2, 4, 10-14, 16, 18-20, 22-23, 32-34, and 90-91. No claims are amended.

As a result of the foregoing actions, claims 36, 44-47, 60-61 68, 88, 92 and 93 remain for examination.

### I. OBJECTION TO SPECIFICATION

The action withdraws the objection to the specification in view of the ADS filed with the response dated April 8, 2011.

### II. MAINTAINED REJECTION UNDER 35 USC § 112, 1ST Paragraph.

#### A. The Rejection (noting only the currently pending claims)

Claims 36, 44-47, 60-61, 68, 88, and 92-93 were rejected for lack of enablement. The specification was considered to be enabling for:

> "A method of treating SIRS in a human subject, the method comprising: obtaining a nucleic acid sample from said subject; assaying said nucleic acid sample to determine the identity of the alleles present at position 4732 of SEQ ID NO: 1; determining that said patient that is homozygous for the C allele or heterozygous for the CT alleles at position 4732 of SEQ ID NO: 1 is at risk for decreased survival and increased multiple organ dysfunction; and administering to said subject activated protein C."

However, the Office maintained that the application does not reasonably enable claims which encompass (a) non-human subjects; (b) any type of inflammatory conditions; (c) any polymorphic site in the protein C gene; (d) any candidate drug known or suspected of being useful for the treatment of an inflammatory condition; (e) any allele (A, T, C, or G) at position 4732 of SEQ ID NO: 1; (f) any genotype in linkage disequilibrium with position 4732 of SEQ ID NO: 1; and (g) any combination of genotypes in linkage disequilibrium ("LD")with position 4732 of SEQ ID NO: 1.

**B. Applicants' Response**

As a result of the cancelations, all of the remaining claims are limited to (a) human subjects (b) systemic inflammatory response syndrome (SIRS), sepsis or septic shock (c) polymorphisms 4732 of SEQ ID NO: 1, 4054 of SEQ ID NO: 2, 2418 of SEQ ID NO: 1, or polymorphisms in LD thereto, or combinations of genotypes in LD thereto (d) activated protein C as the drug (e) the specific alleles for each polymorphism associated with an improved response to activated protein C - as set forth in claim 36.

It appears that the Examiner's only concerns with the present claims would be with an "expansion" to other polymorphisms other than 4732 of SEQ ID NO:1 (*i.e.*, 4054 of SEQ ID NO:2 and 2481 of SEQ ID NO:1 and polymorphisms or combinations of polymorphisms in LD therewith). Therefore, Applicant respectfully submits that the enablement analysis as applied to the present claims should reach the conclusion that undue experimentation would not be required to make and use the presently claimed invention.

In particularly, the nature of the invention is decidedly much more predictable in view of the limitations to particular polymorphisms for which data has been provided in the specification, and those polymorphisms that have a high degree of LD therewith.

With regard to the breadth of the claims, the present claims are limited to human subjects, SIRS, sepsis and septic shock, a limited subset of polymorphisms as represented by specific genotypes, and administration of activated protein C. Accordingly, the breadth of the claims is considerably narrowed from the claims previously considered.

As for guidance in the specification and working examples, examples are provided for each of position 4732 of SEQ ID NO: 1, position 4054 of SEQ ID NO: 2, and position 2418 of SEQ ID NO: 1. Each of these polymorphisms was tested in human subjects given activated protein C and compared to patients not receiving activated protein C.

Applicants respectfully disagree that it is unpredictable that a polymorphism or combination of polymorphisms in LD with established polymorphisms are likely to lack predictive value. On the contrary, it is more likely than not, that such polymorphisms in LD would have predictive value. The present claims are not directed to any polymorphism in the protein C gene, and are directed only to polymorphisms that have a high level of LD with polymorphisms for which data was provided in the spec application as filed.

Similarly, the active claims are limited to human subjects and subjects having SIRS, sepsis, or septic shock. Although the Action notes scientific publications (*i.e.* Landahl and Wall), that point to some of the potential limitations of LD analyses, the cited references are by no means definitive, and represent a limited subset of experience that in many instances does not

undermine the claims presented herein. In particular, Wall acknowledges that there can be weak and strong LD relationships which can affect the ultimate predictability. Furthermore, the issues raised about study design and methods of analyzing data are not particularly relevant to the present discussion.

As to the quantity of experimentation, Applicants respectfully disagree that the present claims would require extensive, undue experimentation; rather any such experimentation would be routine and predictable.

Taking into consideration the limitations previously introduced into the present claims, and the application of the above factors to those claims, it is submitted that the experimentation required to make and use the claimed invention to its full scope would not be undue.

It would therefore be proper to withdraw the rejection from the pending claims.

## III. CONCLUSION

Applicants respectfully request entry of the foregoing cancelations of claims and remarks and submit that these claims and above discussion overcomes all of the pending grounds for rejection. Accordingly, the present claims should now be in condition for allowance.

**Examiner Shaw is respectfully requested to phone the undersigned to discuss any remaining issues that may advance this case rapidly to allowance.**

Respectfully submitted,

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